



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: PROCESS FOR THE PREPARATION OF SUBSTITUTED THIAZOLIDINEDIONE			
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>(I)</p> </div> <div style="text-align: center;"> <p>(II)</p> </div> </div>			
(57) Abstract			
<p>A process for preparing a compound of formula (I, I) or a tautomeric form thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, wherein: J represents O or S; T represents a substituted or unsubstituted aryl group and T<sup>1</sup> is O or S; which process comprises reducing a compound of formula (II, II) or a tautomeric form thereof or a salt thereof or a solvate thereof, wherein T and T<sup>1</sup> are as defined in relation to formula (I), with a complex hydride reducing agent or a source of a complex hydride reducing agent; and thereafter, as required, preparing a pharmaceutically acceptable salt or a pharmaceutically acceptable solvate of the compound of formula (I) or a tautomeric form thereof.</p>			

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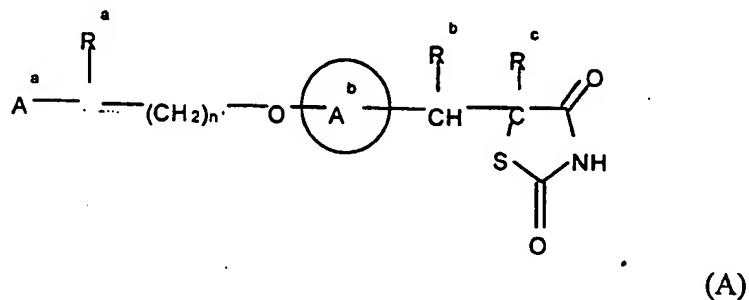
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## PROCESS FOR THE PREPARATION OF SUBSTITUTED THIAZOLIDINEDIONE

This invention relates to a novel process and in particular to a process for preparing certain substituted thiazolidinedione derivatives and to certain intermediates to the substituted thiazolidinedione derivatives

European Patent Application, Publication Number 0306228 discloses certain thiazolidinedione derivatives of formula (A):



or a tautomeric form thereof or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, wherein:

- 15  $A^a$  represents a substituted or unsubstituted aromatic heterocyclyl group;
- $R^a$  represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
- $R^b$  and  $R^c$  each represent hydrogen or  $R^b$  and  $R^c$  together represent a bond;
- 20  $A^b$  represents a benzene ring having in total up to five substituents; and
- $n'$  represents an integer in the range of from 2 to 6.

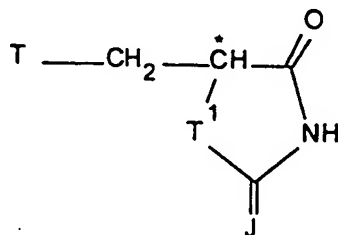
EP 0306228 also discloses a process for reducing the compounds of formula (A) wherein  $R^b$  and  $R^c$  together represent a bond (the 'benzylidene thiazolidine-2, 4-diones') to the corresponding compounds of formula (A) wherein  $R^b$  and  $R^c$  each represent hydrogen (the 'benzylthiazolidine-2, 4-diones'). The particular reduction methods disclosed in EP 0306228 are catalytic hydrogenation methods and dissolving metal reduction methods.

Selective reduction of the exocyclic double bond in the benzylidene thiazolidine-2, 4-dione moiety by complex hydride reducing agents is not considered to provide the basis for a viable commercial process due to a general expectation that the required selectivity would not be achieved, with particular reference to the aluminium hydrides, and/or that the reaction would give poor yields. We have now surprisingly discovered that a benzylidene thiazolidine-2,4-dione group is selectively

reduced to the corresponding benzyl thiazolidine-2,4-dione, by use of a complex hydride reducing agent in a high yielding and commercially viable process.

Accordingly, the present invention provides a process for preparing a compound of formula (I):

5



(I)

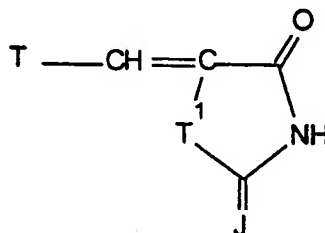
or a tautomeric form thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, wherein:

J represents O or S;

T represents a substituted or unsubstituted aryl group and T<sup>1</sup> is O or S;

which process comprises, reducing a compound of formula (II):

15



(II)

or a tautomeric form thereof or a salt thereof or a solvate thereof, wherein T and T<sup>1</sup> are as defined in relation to formula (I), with a complex hydride reducing agent or a source of a complex hydride reducing agent; and thereafter, as required, preparing a pharmaceutically acceptable salt or a pharmaceutically acceptable solvate of the compound of formula (I) or a tautomeric form thereof.

Suitable complex hydride reducing agents include borohydride reducing agents and aluminium hydride reducing agents.

Suitable borohydride reducing agents include diborane and metal borohydrides.

A suitable metal borohydride is an alkali metal borohydride, such as a lithium, sodium or potassium borohydride, especially lithium or potassium.

Borohydrides include unsubstituted and substituted borohydrides.

Suitable substituted borohydrides include borohydrides with up to three substituents on boron selected from such as alkyl and phenyl groups.

Suitable alkyl groups are C<sub>1-6</sub> alkyl groups, such as ethyl and, especially, butyl groups.

5 Particular butyl groups are *sec* and *tert* butyl groups.

Particular borohydride reducing agents are those which comprise the trihydroborane, triethylborane, tributylborane or triphenylborane moiety.

Favoured borohydride reducing agents include lithium tri-*sec*-butyl borohydride, potassium tri-*sec*-butyl borohydride/lithium chloride, sodium tri-*sec*-butyl borohydride, potassium triphenylborohydride, lithium triethylborohydride,  
10 lithium borohydride and sodium borohydride.

One preferred borohydride reducing agent is lithium borohydride.

One preferred borohydride reducing agent is lithium tri-*sec*-butyl borohydride.

When an unsubstituted metal borohydride is used as the reducing agent, it is  
15 preferred if the reduction is carried out in the presence of a base such as pyridine a substituted pyridine, quinoline, a substituted quinoline, a secondary or tertiary amine, such as piperidine or triethylamine, or a phosphine such as triphenylphosphine.

Conveniently, the said base is used as a solvent or co-solvent for the reaction.

A preferred base is pyridine.

20 A suitable aluminium hydride reducing agent is lithium aluminium hydride.

The reaction conditions for the reduction reaction are the appropriate conditions dictated by the nature of the complex hydride reducing agent chosen:

In one aspect, when the reagent is a borohydride reducing reagent suitable solvents include alkanols, such as methanol and ethanol, tetrahydrofuran and pyridine  
25 or mixtures thereof.

When the reducing reagent is an alkali metal borohydride a preferred solvent is pyridine/tetrahydrofuran.

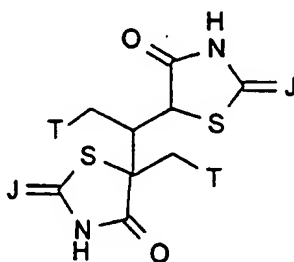
When the reducing reagent is an alkali metal trialkyl or triphenyl borohydride, a preferred solvent is tetrahydrofuran.

30 The borohydride reduction is carried out at a temperature which provides a suitable rate of formation of the required product, usually at ambient or an elevated temperature, suitably at an elevated temperature, preferably above 50°C, for example 65°C and conveniently at the reflux temperature of the required solvent. Usually the reactants are mixed at ambient temperature and the reaction mixture is heated at the  
35 reflux temperature of the solvent.

In a further aspect, when the reagent is an aluminium hydride reducing reagent, suitable solvents include aprotic solvents such as tetrahydrofuran.

The aluminium hydride reduction is carried out at a temperature which provides a suitable rate of formation of the required product, usually at low to ambient temperature, for example a temperature in the range of from -10 to 10°C, suitably in the range of from -5 to 0°C.

- 5 It is considered that the reduction of the compounds of formula (II), wherein T<sup>1</sup> is S, especially when the reducing agent is a borohydride reducing agent, proceeds via an intermediate of formula (III):



(III)

- 10 or a tautomeric form thereof, or salt thereof, or a solvate thereof, wherein J and T are as defined in relation to formula (I).

- The intermediate of formula (III) is obtained in better yield when the reduction is carried out at low temperature. Thus, in a further aspect, the present invention provides a process for preparing a compound of the above defined formula (III), which process comprises, reducing a compound of the above defined formula (II) with a metal hydride reducing agent, preferably a borohydride reducing agent, preferably wherein the reaction is carried at low temperature, suitably below ambient temperature, for example between 0° and 5°C; and thereafter, as required, preparing a salt or a solvate of the compound of formula (III).

A preferred reducing agent for preparing a compound of formula (III) is lithium or potassium tri-*sec*-butylborohydride (also known as "L-selectride" or "K-selectride"), preferably lithium tri-*sec*-butylborohydride.

- 25 The present invention further provides a compound of the above defined formula (III) or a tautomeric form thereof, or salt thereof, or a solvate thereof, which compound is useful as an intermediate.

- The present invention further comprises a process for converting the above defined compound of formula (III) into the above defined compound of formula (I), which process comprises heating the compound of formula (III), suitably in a solvent, and thereafter as required preparing a pharmaceutically acceptable salt or a pharmaceutically acceptable solvate of the compound of formula (I).

Suitable solvents for the said conversion of the compound of formula (III) into compound (I) include those mentioned above for the preparation of the compound of formula (III).

It will be appreciated from the foregoing discussion that the reduction of the compound of formula (II) to provide a compound of formula (I), especially when employing borohydride reducing agents, is preferably carried out at a temperature high enough to ensure conversion of the intermediate of formula (III) into the compound of formula (I), suitably the temperature is above 50°C, for example 65°C and conveniently the reflux temperature of the reaction solvent.

Suitable general reaction conditions for the borohydride and aluminium hydride reductions are also as described in "Reductions by the Alumino- and Borohydrides in Organic Synthesis" by J. Seyden-Penne (VCH Publishers, Inc. / Lavoisier - Tec & Doc, published 1991) and the references disclosed therein.

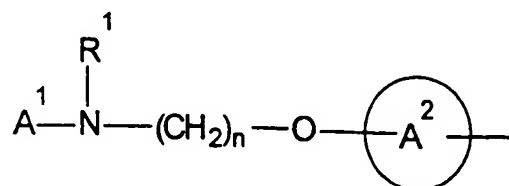
The compounds of formula (I) (or (III)) are isolated from the reaction and subsequently purified by use of conventional isolation and purification methods such as chromatography and crystallization/recrystallization.

The complex hydride reducing agents of the process are usually commercially available or they can be prepared using conventional procedures, for example the borohydride and aluminium hydride reagents can be prepared using methods such as those described in "Reductions by the Alumino- and Borohydrides in Organic Synthesis" (ibid) and particularly in the references cited therein.

Certain of the borohydride reducing agents are conveniently prepared *in situ*. For example, lithium tri-*sec*-butyl borohydride is conveniently prepared from tri-*sec*-butyl borane and lithium aluminium hydride.

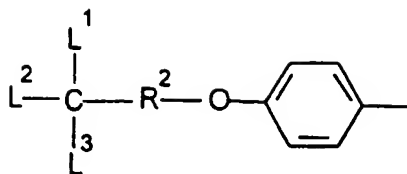
Also, lithium borohydride is conveniently prepared from sodium borohydride and a lithium salt according to known procedures such as those disclosed in Inorg. Chem. 1981, 20, 4454; J. Am. Chem. Soc. 1953, 75, 209; Nature 1954, 173, 125 and J. Am. Chem. Soc. 1955, 77, 6209.

Suitably T represents a moiety selected from the list consisting of (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io), (Ip) and (Iq):



(Ia)

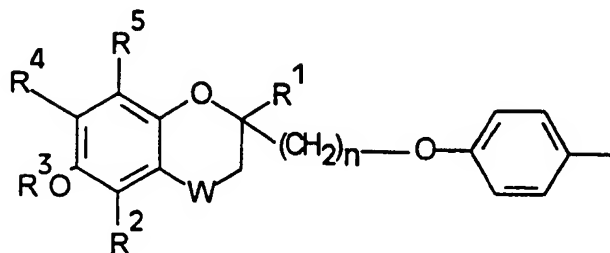
wherein A<sup>1</sup>, A<sup>2</sup>, R<sup>1</sup> and n are as defined in relation to formula (I) of EP 0306228;



(Ib)

wherein  $R^2$ ,  $L^1$ ,  $L^2$  and  $L^3$  are as defined in relation to formula (I) of EP 0008203;

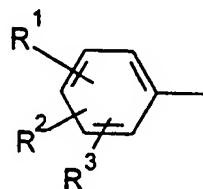
5



(Ic)

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , W and n are as defined in relation to formula (I) of EP 0139421;

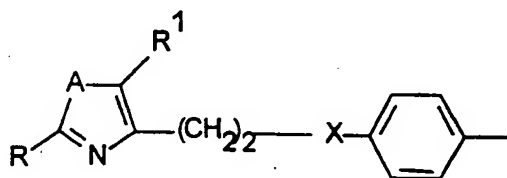
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(Id)

wherein  $R^1$ ,  $R^2$  and  $R^3$  are as defined in relation to formula (I) of EP 0032128;

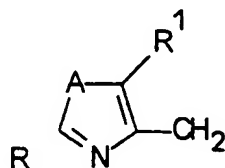
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(Ie)

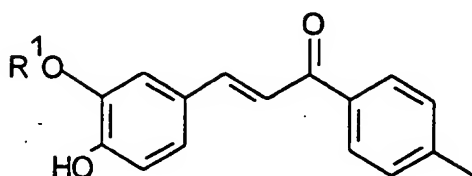
wherein A, R,  $R^1$  and X are as defined in relation to formula (I) of EP 0428312;

20



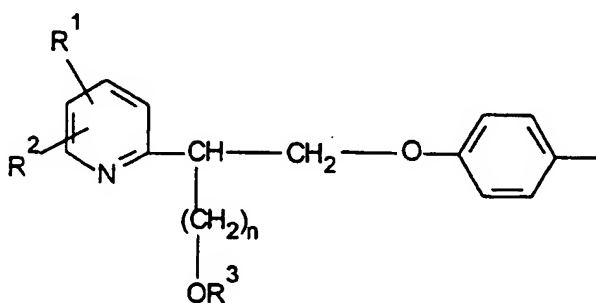
(If)

when A, B, R and R<sup>1</sup> are as defined in relation to formula (II) of EP 0428312;



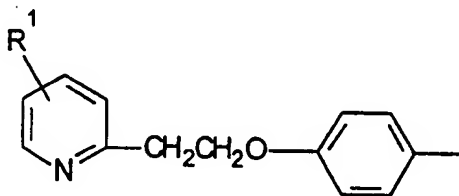
(Ig)

wherein R<sup>1</sup> is as defined in relation to formula (I) of EP 0489663;



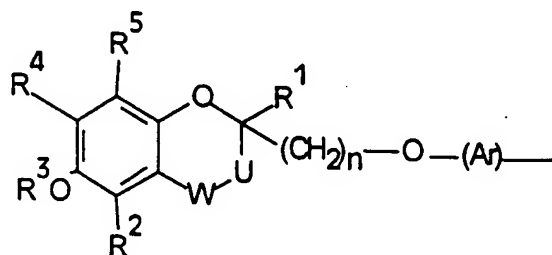
(Ih)

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and n are as defined in relation to formula (I) of EP 0155845;



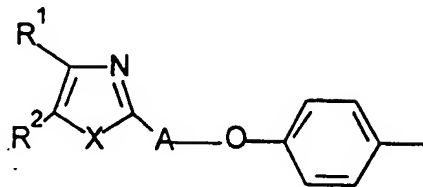
(Ii)

when R<sup>1</sup> is as defined in relation to formula (I) of EP 0257781;



(Ij)

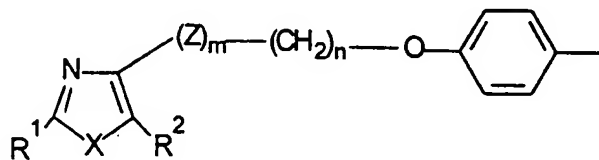
wherein Ar, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, n, U and W are as defined in relation to formula (I) of United States Patent No. 5104888;



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(Ik)

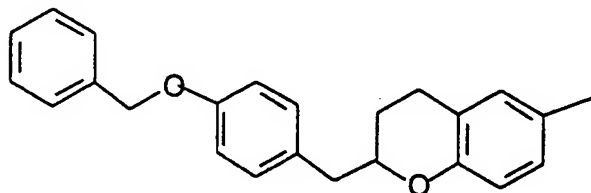
when A, R<sup>1</sup>, R<sup>2</sup> and X are as defined in relation to formula (I) of EP 0208420;



10

(Il)

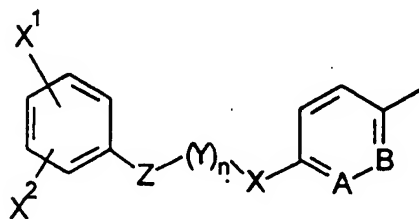
when R<sup>1</sup>, R<sup>2</sup>, X, Z m and n are as defined in relation to formula (I) of EP 0177353;



15

(Im)

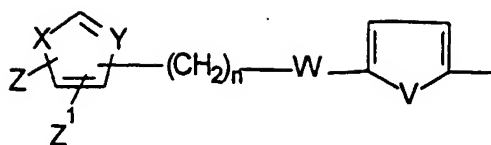
according to formula (I) of EP 0319189;



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(In)

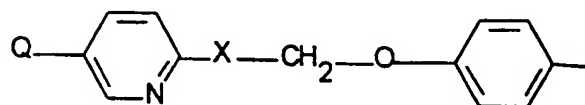
wherein A, B, X, X<sup>1</sup>, X<sup>2</sup>, n and Z are as defined in relation to formula (I) of EP 0332331;



(Io)

wherein V, W, X, Y, Z, Z<sup>1</sup> and n are as defined in EP 0332332; and

5



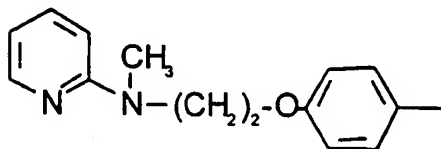
(Ip)

wherein Q and X are as defined in relation to formula (I) of International Application  
10 No. WO 92/18501.

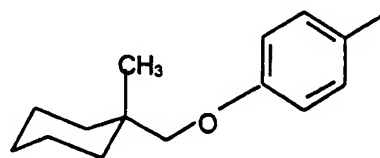
Favourably, T represents a moiety of the above defined formula (Ia), (Ic), (Ie), (If), (Ii), (Ik) or (Io).

In particular T represents a moiety selected from the list consisting of (a), (b), (c), (d), (e), (f), (g), (h) (i) and (j):

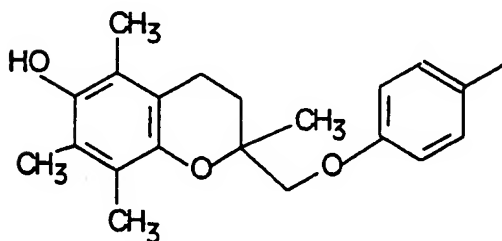
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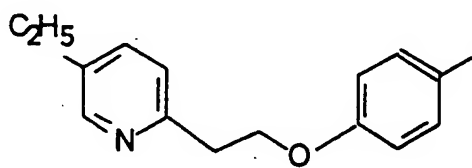
(a),



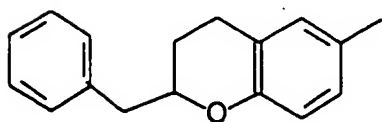
(b)



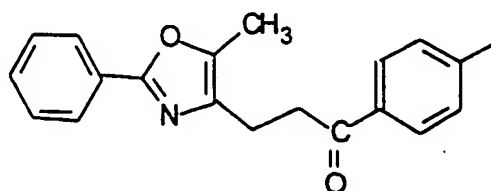
(c)



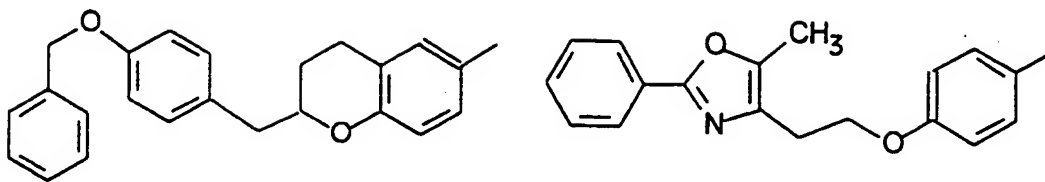
(d)



(e)

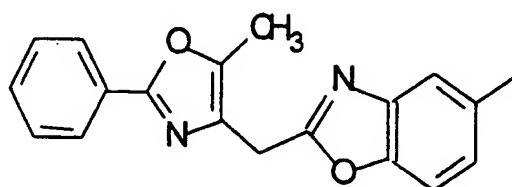


(f)

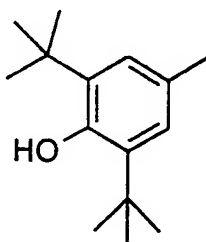


(g)

(h),



(i), and



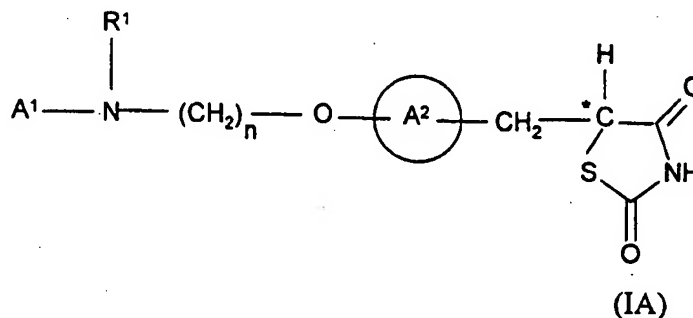
(j).

Preferably, T represents a moiety of the above defined formula (Ia).

Preferably, T<sup>1</sup> represents S.

Preferably J represents O.

Thus, in a preferred aspect, the invention provides a process for preparing a compound of formula (I) as defined in EP 0306228: Accordingly, the invention provides a process for preparing a compound of formula (IA):



or a tautomeric form thereof or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, wherein:

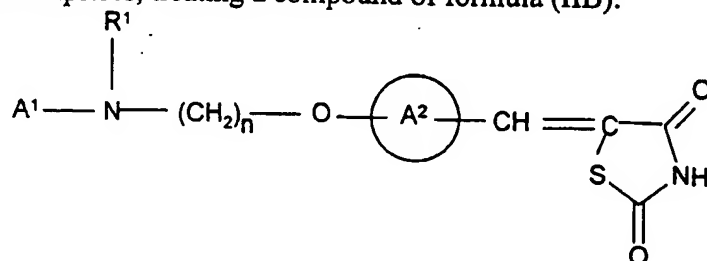
A<sup>1</sup> represents a substituted or unsubstituted aromatic heterocyclyl group;

$R^1$  represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

$A^2$  represents a benzene ring having in total up to five substituents; and

5  $n$  represents an integer in the range of from 2 to 6;

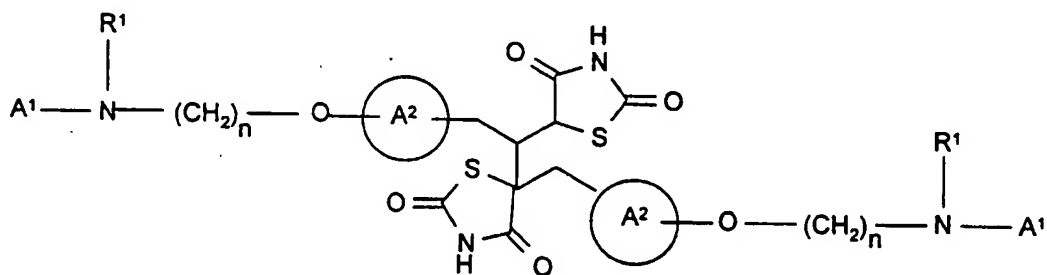
which process comprises, treating a compound of formula (IIB):



(IIB)

10 or a tautomeric form thereof or a salt thereof, or a solvate thereof, wherein  $A^1$ ,  $A^2$ ,  $R^1$  and  $n$  are as defined in relation to formula (IA) with a complex hydride reducing agent or a source of a complex hydride reducing agent, such as a borohydride reducing agent or a source of a borohydride reducing agent; and thereafter, as required, preparing a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate of the compound of formula (IA) or a tautomeric form thereof.

15 In a preferred aspect, the compound of formula (III) is a compound of formula (IIIA):



(IIIA)

20

wherein  $A^1$ ,  $A^2$ ,  $R^1$  and  $n$  are as defined in relation to formula (IA) herein.

Unless mentioned to the contrary herein, the suitable, apt, favoured and preferred values for each variable in the above mentioned moieties of formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io) or (Ip) are as  
25 defined in the European and International patent applications or United States patents mentioned above in respect of each of the said formulae.

In particular, the suitable, apt, favoured and preferred values of the variables  $A^1$ ,  $A^2$ ,  $R^1$  and  $n$  in formulae (IA), (IIB) and (IIIA) are as defined in relation to formula (I) of EP 0306228.

A most preferred value of A<sup>1</sup> in formulae (IA), (IIB) and (IIIA) is a 2-pyridyl group.

A most preferred value of A<sup>2</sup> in formulae (IA), (IIB) and (IIIA) is a moiety of formula:



A most preferred value of R<sup>1</sup> in formulae (IA), (IIB) and (IIIA) is a methyl group.

A most preferred value of n in formulae (IA), (IIB) and (IIIA) is 2.

Most favourably, T represents a moiety of the above defined formula (a), (c) or (d).

A preferred value of T is a moiety of the above defined formula (a).

A most preferred value of formula (IA) is 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-2,4-thiazolidinedione, or a tautomeric form thereof or a salt thereof, or a solvate thereof.

A most preferred value of formula (IIB) is 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}-2,4-thiazolidinedione or a tautomeric form thereof or a salt thereof, or a solvate thereof.

When the reaction comprises a compound of formula (IIB) as substrate it is preferred if the reaction is carried out at an elevated temperature, preferably above 50° C, for example at 65°C.

A preferred example of a compound of formula (IIIB) is 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-5-{1-[2,4-dioxothiazolidin-5-yl]-1-[4-(2-(N-methyl-N-(2-pyridyl)amino)ethoxy)phenyl]methyl}-2,4-thiazolidinedione.

Suitable salts are pharmaceutically acceptable salts.

Suitable solvates are pharmaceutically acceptable solvates.

Unless mentioned to the contrary herein, the suitable, apt, favoured and preferred pharmaceutically acceptable salts, pharmaceutically acceptable solvates and tautomeric forms of each of the compounds in the above mentioned moieties of formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io) or (Ip) are as defined in the European or International patent applications or United States patents mentioned above in respect of each of the said formulae.

In particular it should be mentioned that suitable pharmaceutically acceptable salts include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines

such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-b-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

In addition should be mentioned those pharmaceutically acceptable salts provided by pharmaceutically acceptable acids including mineral acids, for example for compounds of formula (I) wherein T represents a moiety of formula (Ia) suitable salts are those disclosed in WO 94/05659 including salts provided by mineral acids, such as hydrobromic, hydrochloric and sulphuric acids, and organic acids, such as methanesulphonic, tartaric and maleic acids, especially tartaric and maleic acid.

The compounds of formula (II) may be prepared according to known methods, for example by use of the appropriate method disclosed in the abovementioned European and International patent applications or United States patents. The contents of the abovementioned European and International patent applications and United States patents are incorporated herein by reference.

In particular compounds of formula (IIB) may be prepared according to the methods disclosed in EP 0306228.

The following examples illustrate the invention but do not limit it in any way.

Example 1: Preparation of 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-2,4-thiazolidinedione (IA) via reduction of 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}2,4-thiazolidinedione (IIB).

(a) Using lithium tri-sec-butyl borohydride.

A 1M solution of lithium tri-sec-butyl borohydride in tetrahydrofuran (220 ml, 0.22 moles) was added to a suspension of IIB (35.5 g, 0.1 moles) in tetrahydrofuran (310 ml) at 25°C over 30 minutes. The resulting mixture was heated and held at reflux temperature for two and a half hours, and then cooled to 5°C. An aqueous solution of sodium hydroxide (10% w/v, 100 ml, 0.25 moles) was added, followed by 27% aqueous hydrogen peroxide solution (50 ml, 0.4 moles). The resultant solution was stirred at 25°C for three hours, diluted with water (100 ml), and then concentrated via vacuum distillation until a residual volume of 300 ml was achieved. Hydrochloric acid (2.5 M, approx. 200 ml) was added to the rapidly stirred mixture at 20 to 25° C and the resulting precipitate was filtered, washed with water, and dried at 50 dec C in

*vacuo*, to give (IA) (34.4 g). The crude product was recrystallised from 99% IMS (20 ml per g of crude (IA) giving a 79% overall yield.

(b) Using lithium borohydride.

5 A solution of lithium borohydride (67.5g, 3.1mole) in tetrahydrofuran (1.54L) was added *via* cannular to a stirred suspension of (IIB) (500g, 1.4mol) in tetrahydrofuran (950ml) and pyridine (1.13L) at room temperature under nitrogen over 1.5 hours. The mixture was heated to reflux, stirred for 3 hours and cooled to room temperature. The  
10 stirred reaction mixture was quenched into hydrochloric acid (670ml) and water (4.4L) at 8°C over 0.67 hours using tetrahydrofuran (250ml) to wash out residual material. The quench mixture was stirred at 26°C for 0.25 hours, heated to reflux and stirred for 0.75 hours. The hot mixture was allowed to stand for 0.17 hours, filtered through celite, the residue was pulled to dryness and washed with water (500ml). The  
15 aqueous washings were added to the filtrate and stirred at room temperature for 14 hours. The precipitated product was collected by filtration under *vacuo*, pulled to dryness, washed with water (2.8 L) and pulled dry. The damp solid was washed with industrial methylated spirit (2 × 500ml), and dried at 45°C for 72 hours to give (IA) (386.5g, 77%).

20

c) Using sodium borohydride and lithium chloride. (*in-situ* preparation of lithium borohydride)

A solution of sodium borohydride (0.24g, 6.34mmole) in pyridine (5ml) was stirred at  
25 25°C under nitrogen for 0.25 hours then heated to 65°C under reflux. A solution of lithium chloride (0.40g, 9.44mmole) in pyridine (5ml) was added dropwise *via* cannular to the stirred mixture at 65°C which was then held at this temperature for 2 hours, diluted with tetrahydrofuran (20ml) and heated at reflux for a further 0.5 hours. The mixture was cooled to 30°C, (IIB) (1.0g, 2.82mmole) was added in portions and  
30 the reaction mixture was heated to reflux for 4 hours. A solution of hydrochloric acid (1ml) and water (10ml) was added dropwise to the reaction mixture at 5°C. The mixture was concentrated in *vacuo*, pyridine (4ml) and water (6ml) were added and the mixture was stirred at 5°C with the pH being adjusted to 6 using hydrochloric acid. Water (10ml) was added and the mixture was stirred for 15 hours. The  
35 suspension was filtered, the residue was washed with water (10ml), pulled dry and dried at 50°C for 24h to give (IA), (0.88g, 88%).

Example 2: Preparation of 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-2,4-thiazolidinedione (IA) via reduction of 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}2,4-thiazolidinedione (IIB), using lithium aluminium hydride.

5 To a suspension of lithium aluminium hydride (1.13 g, 1 mole equivalent) in tetrahydrofuran (200 ml) at 0°C was added (IIB) (10 g, 1 mole equivalent) in portions over 15 minutes. The temperature was kept below 5°C during the addition. The mixture was stirred at 0°C for 30 minutes, and then at 10°C until the reaction was  
10 judged to be complete by HPLC (1.75 hours). The solution yield of (IA) was 69%.

Example 3: Preparation of 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-5-{1-[2,4-dioxothiazolidin-5-yl]-1-[4-(2-(N-methyl-N-(2-pyridyl)amino)ethoxy)phenyl]methyl}-2,4-thiazolidinedione (IIIA) from 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}2,4-thiazolidinedione (IIB).

To a solution of compound (IIB) (3.56 g) in tetrahydrofuran (THF, 120 ml) at -5 to 0°C was added a 1M solution of lithium tri-*sec*-butylborohydride (L-selectride) in THF (22 ml). The resulting mixture was stirred for 40 minutes, and then cooled to -  
20 10°C to stop the reaction. Sodium hydroxide solution (10% w/w, 40 ml) was carefully added, followed by aqueous hydrogen peroxide (27% w/w, 10 ml) to ensure destruction of the borohydride reagent. THF was removed in vacuo, and the aqueous mixture was neutralised to pH 7 using 2M hydrochloric acid. The resulting solid was  
25 filtered and discarded, and the filtrate was cooled to 4°C. After standing overnight a second crop of solid was obtained and this was purified twice by flash column chromatography using dichloromethane/methanol as eluent. Compound (IIIC) was isolated as white crystals (109 mg, 3% isolated yield).

Example 4. Preparation of 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidine-2,4-dione (ID) via reduction of 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzylidene}-2,4-thiazolidine-2,4-dione (IID).

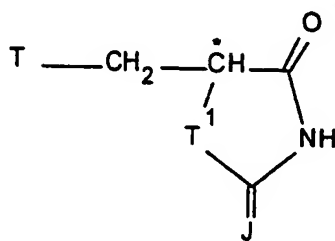
A 2.0 M solution of lithium borohydride in tetrahydrofuran (31 ml, 62.0 mmol) was added dropwise to a stirred suspension of 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzylidene}-2,4-thiazolidine-2,4-dione (10.0 g, 28.22 mmol) in tetrahydrofuran (19 ml) and pyridine (23 ml)  
35 at 30°C under nitrogen. The resulting mixture was heated under reflux for 4 h (reaction monitored by HPLC) and then cooled to ambient temperature and added dropwise to an efficiently stirred solution of conc. hydrochloric acid (13.5 ml) in water (88.7 ml) between

10°C and 20°C. The resulting orange suspension was heated to reflux temperature and held for 30 minutes and then cooled to ambient temperature. The resulting suspension was stirred for 30 minutes and the product was collected by filtration and washed with water (20 ml x 3). The crude product was heated to reflux in acetic acid (50 ml) and charcoal was added  
5 (1.5 g) to the resulting solution, which was then diluted with ethanol (50 ml), filtered through celite, and the celite bed washed through with hot ethanol (50 ml). The filtrate and washings were combined and allowed to cool to 5°C resulting in crystallisation of a white solid which was isolated by filtration to give compound (ID) (5.29 g, 53%). A second crop of material was obtained by partial concentration of the mother liquor (0.81 g, 8.1%).

10

## Claims:

1. A process for preparing a compound of formula (I):



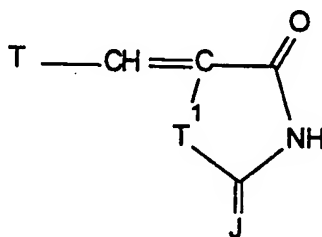
(I)

or a tautomeric form thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, wherein:

10 J represents O or S;

T represents a substituted or unsubstituted aryl group and T<sup>1</sup> is O or S;

which process comprises, reducing a compound of formula (II):



(II)

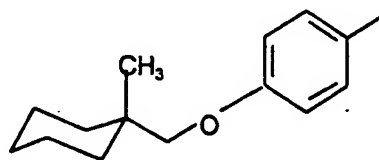
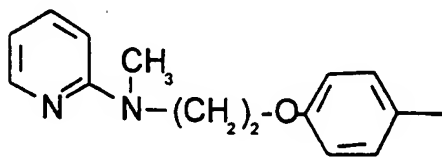
or a tautomeric form thereof or a salt thereof or a solvate thereof, wherein T and T<sup>1</sup> are as defined in relation to formula (I), with a complex hydride reducing agent or a source of a complex hydride reducing agent; and thereafter, as required, preparing a pharmaceutically acceptable salt or a pharmaceutically acceptable solvate of the compound of formula (I) or a tautomeric form thereof.

2. A process according to claim 1, wherein the complex hydride reducing agent is a borohydride reducing agents or an aluminium hydride reducing agent.

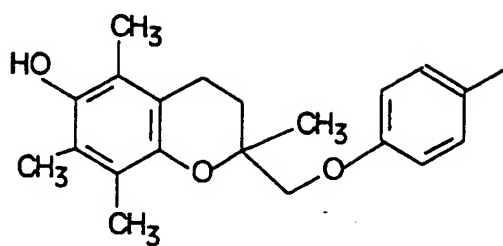
3. A process according to claim 2, wherein the borohydride reducing agent is diborane or a metal borohydride.

4. A process according to claim 3, wherein the metal borohydride is an alkali metal borohydride.

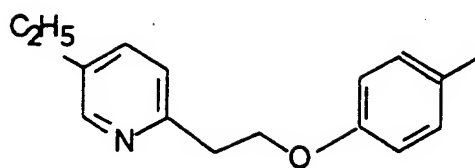
5. A process according to claim 3 or claim 4, wherein the metal borohydride is lithium, sodium or potassium borohydride.
6. A process according to any one of claims 3 to 5, wherein the metal borohydride is an unsubstituted or a borohydride in which the boron is substituted with up to three substituents selected from alkyl and phenyl.
7. A process according to any one of claims 3 to 6, wherein the metal borohydride is selected from the list consisting of: lithium tri-sec-butyl borohydride, potassium tri-sec-butyl borohydride, sodium tri-sec-butyl borohydride, potassium triphenylborohydride, lithium triethylborohydride, lithium borohydride and sodium borohydride.
8. A process according to claim 2, wherein the complex hydride reducing agent is an unsubstituted borohydride and the reaction is carried out in the presence of a base.
9. A process according to claim 8, wherein the base is pyridine, a substituted pyridine, quinoline, a substituted quinoline, a secondary or tertiary amine or a phosphine.
10. A process according to claim 8 or claim 9, wherein the base is used as a solvent or co-solvent for the reaction.
11. A process according to any one of claims 8 to 11, wherein the base is pyridine.
12. A process according to claim 2, wherein the aluminium hydride reducing agent is lithium aluminium hydride.
13. A process according to any one of claims 1 to 12, wherein T represents a moiety selected from the list consisting of (a), (b), (c), (d), (e), (f), (g), (h) (i) and (j):



(a),

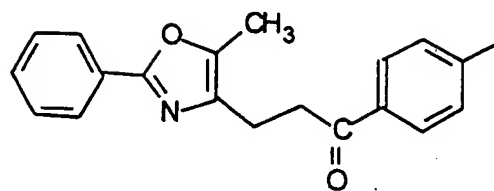
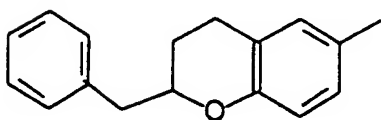


(b)



(c)

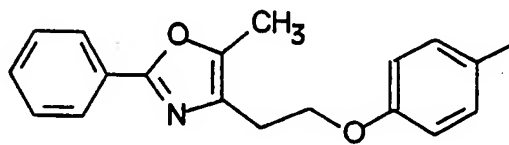
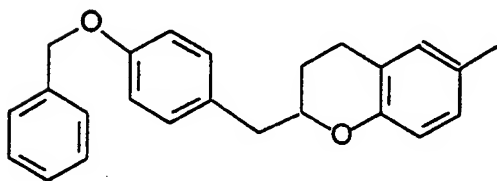
(d)



(e)

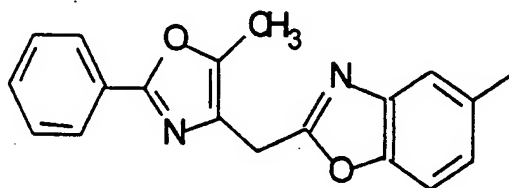
(f)

5

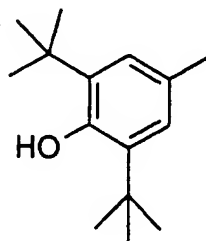


(g)

(h),



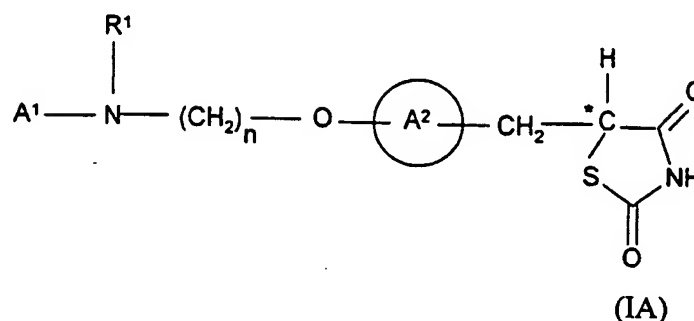
(i), and



(j).

14. A process according to any one of claims 1 to 13, wherein T<sup>1</sup> represents S and J represents O.

15. A process according to claim 1, for preparing a compound of formula (IA):



or a tautomeric form thereof or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, wherein:

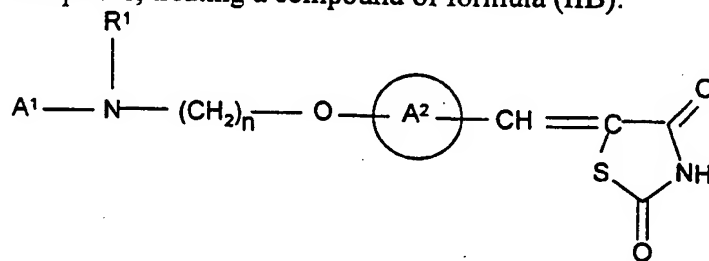
A<sup>1</sup> represents a substituted or unsubstituted aromatic heterocyclyl group;

R<sup>1</sup> represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

A<sup>2</sup> represents a benzene ring having in total up to five substituents; and

n represents an integer in the range of from 2 to 6;

which process comprises, treating a compound of formula (IIB):

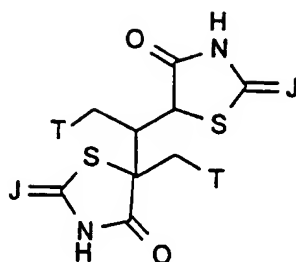


(IIB)

or a tautomeric form thereof or a salt thereof, or a solvate thereof, wherein A<sup>1</sup>, A<sup>2</sup>, R<sup>1</sup> and n are as defined in relation to formula (IA) with a complex hydride reducing agent or a source of a complex hydride reducing agent; and thereafter, as required, preparing a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate of the compound of formula (IA) or a tautomeric form thereof.

16. A process according to claim 15, wherein (IA) is 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-2,4-thiazolidinedione, or a tautomeric form thereof or a salt thereof, or a solvate thereof and (IIB) is 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene}-2,4-thiazolidinedione or a tautomeric form thereof or a salt thereof, or a solvate thereof.

17. A compound of formula (III):



(III)

5 or a tautomeric form thereof, or salt thereof, or a solvate thereof, wherein J and T are as defined in relation to formula (I) in claim 1.

18. A compound according to claim 17, being 5-{4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl}-5-{1-[2,4-dioxothiazolidin-5-yl]-1-[4-(2-(N-methyl-N-(2-pyridyl)amino)ethoxy)phenyl]methyl}-2,4-thiazolidinedione.

19. A compound according to claim 17 or 18, for use as an intermediate.

20. A process for preparing a compound of formula (I) according to claim (I) which process comprises:

(a) reducing a compound of formula (II), as defined in claim 2, with a metal hydride reducing agent at low temperature, optionally isolating the compound of formula (III); and/or

(b) heating a compound of formula (III) to provide the compound of formula (I); and thereafter as required preparing a pharmaceutically acceptable salt or a pharmaceutically acceptable solvate of the compound of formula (I).

# INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/EP 98/00818

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D277/34 C07D417/12 C07D417/06 C07D417/10 C07D417/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 115, no. 17, 28 October 1991 Columbus, Ohio, US; abstract no. 183284f, page 926; XP002066776 see abstract & JP 03 077 875 A (KAKEN PHARMACEUTICAL CO LTD) 3 April 1991 ---	1-8
A	EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 cited in the application see page 8, line 41 - page 8, line 49; claims; example 7 --- -/--	1-20



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- "&" document member of the same patent family

Date of the actual completion of the international search

3 June 1998

Date of mailing of the international search report

06/07/1998

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Authorized officer

Henry, J

## INTERNATIONAL SEARCH REPORT

Int .tional Application No

PCT/EP 98/00818

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 13095 A (THE UPJOHN COMPANY) 8 July 1993 see claims ---	1-20
A	EP 0 454 501 A (SANKYO COMPANY LIMITED) 30 October 1991 see page 19 - page 23 see page 25, line 31 - page 26, line 35; claims 47, 48 -----	1-20

# INTERNATIONAL SEARCH REPORT

Information on patent family members

In ternational Application No

PCT/EP 98/00818

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